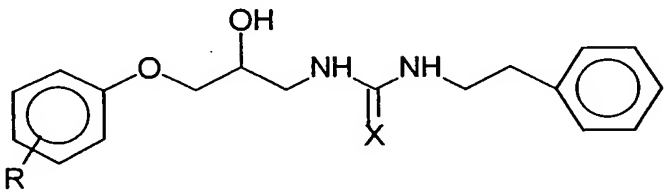
450/NF/03

NOVEL N-ARYLOXYPROPANOLYL-N'-PHENETHYL-UREA

Field of the invention

The presently invention relates to novel n-aryloxypropanolyl-N'-phenethyl-urea. The present invention particularly relates to the synthesis of novel N-aryloxypropanolyl-N'-phenethyl-urea derivatives of formula **3** and their use as potent appetite suppressants for treatment of obesity



Formula 3

wherein R is selected from the group consisting of H, 2, 3 or 4-trifluoromethyl, 2, 3, or 4-chloro, 2, 3, or 4-bromo, 4-acetyl, 4-propionyl, 4-acetamido, 2,3 or 4 methoxy, 4 nitrile, 2,3 or 4-methyl , and 4 formyl and X is S or O.

Background of invention

Obesity is now a common disorder in the industrialized as well as in the developing countries. It is estimated that somewhere between 34 and 61 million people in the USA are obese and in much of the developing countries the incidence is increasing by about 1% per year. It is responsible for various adverse effects on health being associated with an increase in morbidity and mortality from diabetes, hypertension, cardiovascular diseases and certain forms of cancer.

There are only two drugs currently available for the long term treatment of obesity in United States .One of these, sibutramine (Ryan,D.H., Kaiser,P., Bray, G.A. *Obes.Res.***1995**,3:553S-9S; Jones,S.P., Smith, I.G.,Kelly, F.,Gray,J.A. *Int J Obes Relat Metab Disord* **1995**,19:41), the only F D A approved drug, suppresses appetite by altering norepinephrine and 5HT metabolism in the brain .The other drug, orlistat (*Int J Obes Relat Metab disord* **1997**,21:S12-S23), reduces fat absorption by inhibiting gastric, pancreatic and other gastrointestinal lipases. The results of long-term clinical trials, extensive information of clinical effectiveness and side effects, however indicate that both of these drugs are of limited efficacy (Hill,J.O., Haupman,J., Asnderson,J.W. *Am J Clin Nutr* **1999**,69:1108-16; Sjostrom,L., Rissanen,A., Anderson,T. *Lancet* **1998**,352:167-172; Davidson, M.H., Hauptman,J., DiGirolamo, M.etal, *J Am Med Assoc* **1999**,281:235-42; Hollander, P.A.,Elbein, S.C., Hirsch,I.B.etal *Diabetes Care* **1998**,21:1288-94;Kaiser,P.E. & Hinson, J.L. J Clin. Pharmacol **1994**, 34,1019; Bray, G.A. *Obes Res* 7,**1999**,189-198; Fanghanel, G.,

Cortinas, L., Sanchez-Reyes, L., Berber,A., Int.J.Obes. **2000**, 24(2), 144-150; Cuellar,Guillermina,Elisa Martinez; Ruiz,Alberto Martinez; Monsalve,Maria Cristina Revilla, Berber,Arturo, Obes. Res. **2000**, 8(1), 71-82).

Objects of the invention

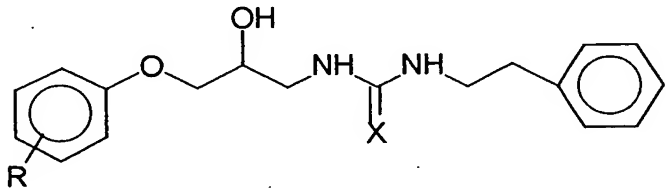
The main object of the invention is to provide novel N-aryloxypropanolyl-N'-phenethyl ureas useful as appetite suppressant.

Another objective of the invention is to provide a process for the preparation of novel N-aryloxypropanolyl-N'-phenylethyl ureas which are useful as appetite suppressants.

Summary of the invention

The present invention relates to the novel N-aryloxypropanolyl-N'-phenylethyl ureas. These compounds are potentially useful in the treatment of obesity.

Accordingly the present invention relates to a novel N-aryloxypropanolyl-N'-phenethyl urea of general formula **3** wherein R is selected from the group consisting of H, 2, 3 or 4-trifluoromethyl, 2, 3, or 4-chloro, 2, 3, or 4-bromo, 4-acetyl, 4-propionyl, 4-acetamido, 2,3 or 4 methoxy, 4 nitrile, 2,3 or 4-methyl and 4- formyl and X is S or O.



Formula 3

In one embodiment of the invention, representative compounds of formula 3 are selected from the group consisting of:

3a. N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-urea.

3b. N-[2-hydroxy-3-phenoxypropyl]-N'-2-phenethyl-urea

3c. N-[2-hydroxy-3-(3-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-urea.

3d. N-[3-(4-chlorophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3e. N-[3-(4-bromophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3f. N-[3-(4-acetylphenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3g. N-[2-hydroxy-3-(4-propionylphenoxy)propyl]-N'-2-phenethyl-urea.

3h. N-[3-(4-acetamidophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3i. N-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3j. N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3k. N-[3-(4-cyanophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3l. N-[2-hydroxy-3-(2-methylphenoxy)propyl]-N'-2-phenethyl-urea.

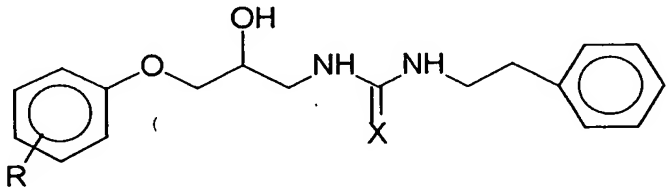
3m. N-[2-hydroxy-3-(3-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3n. N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-thiourea

3o. N-[2-hydroxy-3-(4-propionylphenoxy)propyl]-N'-2-phenethyl-thiourea.

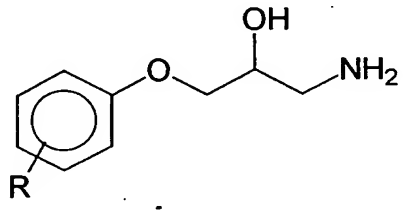
3p. N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-thiourea.

The invention also provides a process for the preparation of N-aryloxypropanolyl-N'-phenethyl urea derivatives of the formula **3** wherein X is S or O and R is selected from the group consisting of H, 2, 3 or 4-trifluoromethyl, 2, 3, or 4-chloro, 2, 3, or 4-bromo, 4-acetyl, 4-propionyl, 4-acetamido, 2,3 or 4 methoxy, 4 nitrile, 2,3 or 4-methyl and 4- formyl,



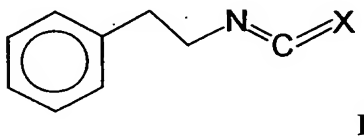
Formula 3

the process comprising reacting a substituted phenolic compound with epichlorohydrin in the presence of alkali carbonate to obtain the corresponding phenoxy epoxy propane which is then reacted with ammonium hydroxide to obtain aminoalcohol of formula 1



Formula 1

wherein R is as given above, which is then reacted with a cyanate compound of formula 2 wherein X is oxygen or sulphur



Formuala 2

to obtain the compound of formula 3.

In one embodiment of the invention the alkali carbonate is selected from K_2CO_3 and Na_2CO_3.

In another embodiment of the invention the reaction between compound of formula 1 and compound of formula 2 is carried out in an aprotic solvent selected from the group consisting of CH_3CN, $CHCl_3$, CH_2Cl_2. THF and 1,2-Dichloroethane.

In another embodiment of the invention the reaction between compound of formula 1 and compound of formula 2 is carried out at a temperature in the range of 15-50°C for a period ranging between 5-18 hrs.

In another embodiment of the invention the reaction between compound of formula 1 and compound of formula 2 is carried out in equimolar proportions of compound 1and compound 2.

The present invention also relates to a pharmaceutical composition comprising compound of formula 3 with one or more conventional additives.

The present invention also relates to a method for the treatment of obesity comprising administering to a subject suffering from obesity, a pharmaceutically effective amount of compound of formula 3.

In one embodiment of the invention, the compound of formula 3 is administered in the form of a pharmaceutical composition of compound of formula 3 with pharmaceutically acceptable additives.

The present invention also provides relates to the use of compound of formula 3 alone or with one or more pharmaceutically acceptable excipients for the treatment of obesity.

In another embodiment of the invention, N-[2-hydroxy-3-[4-trifluoromethylphenoxy] propyl]-N'-2-phenethylurea (**3a**) shows same activity as Sibutramine.

In another embodiment of the invention (N -[2-hydroxy-3-(4-trifluoromethylphenoxy) propyl]-N'-2-phenethyl-urea, showed a decrease of 41.42% in food intake as compared to food intake in the control group.

In another embodiment of the invention, (N -[2-hydroxy-3-(4- methoxyphenoxy) propyl]-N'-2-phenethyl-urea (compound **3j**), showed decrease of 31.82% in food intake as compared to food intake in the control group.

In another embodiment of the invention (N - [2-hydroxy-3-(4-trifluoromethylphenoxy) propyl]-N'-2-phenethyl-thiourea (compound **3n**), showed decrease of 28.4% in food intake as compared to food intake in the control group.

In another embodiment of the present invention the compound of formula 3 did not cause any significant change in water intake and gross behaviour.

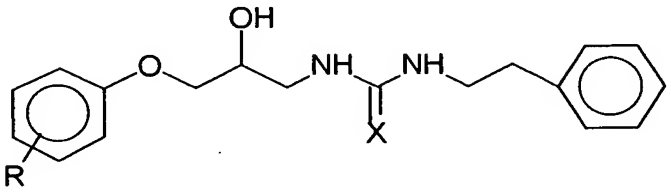
Brief description of the accompanying drawing

Figure 1 illustrates the reaction scheme of the process of the invention.

Detailed description of the invention

The present invention provides a novel N-aryloxypropanolyl-N'-phenethyl urea of general formula **3** wherein R is selected from the group consisting of H, 2, 3 or 4-

trifluoromethyl, 2, 3, or 4-chloro, 2, 3, or 4-bromo, 4-acetyl, 4-propionyl, 4-acetamido, 2,3 or 4 methoxy, 4 nitrile, 2,3 or 4-methyl and 4- formyl and X is S or O.



Formula 3

Representative compounds of formula 3 include:

3a. N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-urea.

3b. N-[2-hydroxy-3-phenoxypropyl]-N'-2-phenethyl-urea

3c. N-[2-hydroxy-3-(3-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-urea.

3d. N-[3-(4-chlorophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3e. N-[3-(4-bromophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3f. N-[3-(4-acetylphenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3g. N-[2-hydroxy-3-(4-propionylphenoxy)propyl]-N'-2-phenethyl-urea.

3h. N-[3-(4-acetamidophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3i. N-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3j. N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3k. N-[3-(4-cyanophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea.

3l. N-[2-hydroxy-3-(2-methylphenoxy)propyl]-N'-2-phenethyl-urea.

3m. N-[2-hydroxy-3-(3-methoxyphenoxy)propyl]-N'-2-phenethyl-urea.

3n. N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-thiourea

3o. N-[2-hydroxy-3-(4-propionylphenoxy)propyl]-N'-2-phenethyl-thiourea.

3p. N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-thiourea.

The process of preparation of the compound of formula 3 comprises reacting a substituted phenolic compound with epichlorohydrin in the presence of alkali carbonate to obtain the corresponding phenoxy epoxy propane. This is then in turn reacted with ammonium hydroxide to obtain aminoalcohol of formula 1 where R is as given above. The amino alcohol of formula 1 is then reacted with a cyanate compound of formula 2 where X is oxygen or sulphur. This reaction is preferably carried out at a temperature in the range of 15-50°C for a period ranging between 5-18 hrs. to obtain the compound of formula 3.

The alkali carbonate is selected from K_2CO_3 and Na_2CO_3 The reaction between compound of formula 1 and compound of formula 2 is carried out in an aprotic solvent such as CH_3CN, $CHCl_3$, CH_2Cl_2. THF and 1,2-Dichloroethane.

For example, compounds of the formula (**3**) can conveniently be made according to the general synthetic route outlined in the Scheme given in the accompanying drawing.

The 1-amino-3-aryloxypropan-2-ol of the general formula **1** can be prepared by methods known in the art of preparing analogous compounds eg. by condensing the appropriately substituted phenol with epichlorohydrin in the presence of K_2CO_3 / Na_2CO_3 to give the corresponding aryloxy epoxy propane which in turn were reacted with NH_4OH to furnish the aminoalcohol of the general formula **1**. The process used for this invention comprises of the reaction of one mole equivalent of 1-amino-3-aryloxypropan-2-ol of the general formula **1**, R=H, 2,3 or 4-trifluoromethyl, 2,3,4-chloro, 2,3,4-bromo, 4-acetyl, 4-propionyl, 4-acetamido, 2 ,3 or 4 methoxy, 4 nitrile, 2,3 or 4-methyl , and 4 formyl with phenylethyl isocyanate(1.5 mole) / phenethylisothiocyanate (1 mole) of the general formula **2**, in an aprotic, polar solvent in the temperature range of 25° to 30°C for a period range of 5 to 15 hrs to give the corresponding urea (X=O) / thiourea (X=S) derivatives of the formula **3** in the accompanying drawing and isolating the compounds by conventional methods .

It was observed that N-[2-hydroxy-3-[4-trifluoromethylphenoxy] propyl]-N'-2-phenethylurea (**3a**) shows the same activity as Sibutramine. (N -[2-hydroxy-3-(4-trifluoromethylphenoxy) propyl]-N'-2-phenethyl-urea, showed significant decrease of 41.42% in food intake as compared to food intake in control group. (N -[2-hydroxy-3-(4-methoxyphenoxy) propyl]-N'-2-phenethyl-urea (compound **3j**), showed significant decrease of 31.82% in food intake as compared to food intake in control group. (N - [2-hydroxy-3-(4-trifluoromethylphenoxy) propyl]-N'-2-phenethyl-thiourea (compound **3n**), showed significant decrease of 28.4% in food intake as compared to food intake in control group. The compound of formula 3 did not cause any significant change in water intake and gross behaviour.

The following examples are given by the way of illustration and should not be construed to limit the scope of present invention.

Example 1: ***1-(4-trifluoromethylphenoxy)-2,3-epoxypropane:***

A mixture of 4-trifluoromethyl phenol (2g), K_2CO_3(2.04g) and epichlorohydrin (10mL) was stirred at 120°C for 4 hrs. After completion of reaction, the solid was filtered, filtrate was Diluted with water (50mL) and extracted with ethylacetate (3×25mL). Organic layer was washed with Distilled water (3×100mL) and concentrated to an oil, which was purified on silica gel column using hexane: ethylacetate (9:1) as eluant, to give required compound 2.42g (90%) yield.

^{1}HNMR(200MHz,$CDCl_3$): δ 2.75-2.79(m,1H,C-3H), 2.90-2.95 (m,1H,C-3H), 3.34-3.38 (m,1H,C-2H), 3.93-4.01 (dd,1H,J=11.0Hz,J=5.8Hz,C-1H), 4.26 –

4.33(dd,1H,J=11.1Hz,J=2.9Hz,C-1H), 6.96-7.00 (d,2H,J=8.5Hz,2&6-ArH), 7.52-7.57 (d,2H,J=8.6 Hz,3&5ArH).

MS(m/z) : 218 (M^+,100%),199,188.

Similarly other substituted aryloxyepoxypropane were prepared substituting the 4-trifluoromethyl phenol by an equivalent amount of substituted phenol (*J. Med .Chem* **1972**,15 ,No.3,286-291.)

Example 2: ***3-amino-1-(4-trifluoromethylphenoxy) propan-2-ol(1):***

A solution of 1-(4-trifluoromethylphenoxy)-2,3-epoxy propane (2g) in MeOH (10mL) was stirred with NH_4OH (60mL) at room temperature (18°C) for 24 hrs. The turbid solution was filtered through sintered and filtrate was concentrated. The aqueous layer thus obtained was extracted with CH_2Cl_2 (3× 25mL). Combined organic extracts dried (Na_2SO_4) and concentrated to an oil which solidified, 1.68g (74%),m.p 75-77°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 1.18(bs,2H,NH_2), 2.74-2.95(m,2H,$C\underline{H}_2NH_2$),3.81-4.03(m,4H,OCH_2,C<u>H</u>OH andOH), 6.89-6.93 (d,2H,J=8:7Hz,ArH adjacent to 0), 7.45-7.49 (d,2H,J=8.7Hz,ArH adjacent to CF_3).

MS (m/z) : 236 ($(M+1)^+$,100%),221,207.

Similarly other substituted phenoxy propanolamines (1a-m) were prepared by substituting the 1-(4-trifluoromethtylphenoxy)-2,3-epoxypropane with an equivalent amount of 1-(substituted phenoxy)-2,3-epoxypropanes, (Terent'ev , A. P. ; Volodina, M. A. ; Smirnova, M. L. ; Mishina, V. G. , Zhur. Obshchei Khim. 29, 3478-82, 1959)

Example3:N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl]-N'-2-phenethyl-Urea (3a)

To a stirred solution of 3-amino-1-(4-trifluoromethylphenoxy) propan-2-ol (0.235g, 1mmol.) in CH_3CN (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 25°C for 12 hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$:MeOH (99:1)as the eluant, yield 74%, m.p. 78-80^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.81-2.84(t,2H,J=6.7Hz,$ArC\underline{H}_2$), 3.41-3.48(m,4H,NCH_2) 3.9-4.2(m,3H,$OC\underline{H}_2$,C<u>H</u>OH), 6.93-6.97(d,2H,J=8.4Hz,ArH adjacent to O), 7.16-7.36(m,5H, ArH), 7.52-7.56 (d,2H,J=8.6Hz,ArH adjacent to CF_3)

MS(m/z): 383 ($(M+1)^+$,100%), 329, 236.

Example 4: N-[2-hydroxy –3- phenoxypropyl]-N'-2-phenethylurea(3b)

To a stirred solution of 3-amino-1-phenoxy-propan–2-ol (0.167g, 1mmol.)in CH_3CN (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes

Mixture was stirred at 25°C for 10 hrs. till all the amine was consumed. Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield 85 %. m p 108°C.

^{1}HNMR(200MHz, $CDCl_3$) : δ 2.81-2.84 (t,2H,J=6.8Hz,ArC<u>H</u>$_2$),3.41-3.50 (m,4H,NC<u>H</u>$_2$), 3.92-4.1(m,3H,OC<u>H</u>$_2$-C<u>H</u>OH), 6.87 –6.91 (m,3H,2,4,6-OArH), 7.21-7.26(m,7H,ArH).

MS (m/z) : 315 ($(M+1)^+$,100%),168.

<u>Example 5:</u>N-[2-hydroxy-3-(3-trifluoromethylphenoxy) propyl]-N'-2-phenethyl-urea (3c)

To a stirred solution of 3-amino-1-(3-trifluoromethylphenoxy) propan-2-ol (0.235g, 1mmol.)in THF (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 24°C for 12hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$ as the eluant, yield -33%.

^{1}HNMR (200MHz,$CDCl_3$) : δ 2.78-2.85(t,2H,J=6.8Hz,ArC<u>H</u>$_2$), 3.35-3.56(m,4H, NC<u>H</u>$_2$), 3.94-4.10(m,3H,,OC<u>H</u>$_2$-C<u>H</u>-OH), 7.04-7.88 (m,9H,ArH)

MS(m/z) : 383 ($(M+1)^+$,100%),236.

<u>Example 6:</u> N-[3-(4-chlorophenoxy)-2-hydroxy propyl]-N'-2-phenethyl-urea(3d)

To a stirred solution of 3-amino-1-(4-chlorophenoxy) propan–2-ol (0.2015 g, 1mmol.)in CH_3CN (4mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes .Mixture was stirred at 26°C for 10hrs.till all the amine was consumed. Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield 41 %. m p 100-101°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.77-2.84(t,2H,J=6.8Hz, ArC<u>H</u>$_2$), 3.26-3.54(m,4H,NC<u>H</u>$_2$), 3.87-4.05(m,3H,OC<u>H</u>$_2$-C<u>H</u>-OH), 6.79-6.84(d,2H,J=8.9Hz,ArH adjacent to O), 7.16-7.34 (m,7H,ArH).

MS(M/Z) : 351 ($(M+1)^+$,17%),349(M^+,55%).

<u>Example 7</u>: *N-[3-(4-bromophenoxy)-2-hydroxypropyl]-N'-2-phenethyl-urea(3e)*

To a stirred soln of 3-amino-1-(4-bromophenoxy) propan–2-ol (0.246 g, 1mmol.)in CH_3CN (5mL) was added phenethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes. Mixture was stirred at 27°C for 5hrs.till all the amine was consumed Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield 57 %. m p 115-116°C.

^{1}HNMR(200MHz, $CDCl_3$) : δ 2.77-2.84(t,2H,J=6.8Hz,ArCH_2), 3.26-3.62(m,4H,NCH_2), 3.88-4.02(m,3H,OCH_2-CH-OH), 6.75 –6.79(d,2H,J=8.7Hz,ArH adjacent to O), 7.16-7.39(m,7H,ArH).

MS (m/z) : 393 (M^+,100%), 395($(M+2)^+$,97%).

Example 8:N-[3-(4-acetylphenoxy)-2-hydroxy propyl]-N'-2-phenethy-lurea(3f)

To a stirred solution of 3-amino-1-(4-acetylphenoxy) propan-2-ol (0.209g, 1mmol.)in 1,2-dichloroethane (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 26°C for 13 hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$:MeOH (99:1) as the eluant, yield 39%, m.p. 95^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.54- (s,3H,$COCH_3$), 2.75-2.82(t,2H,J=6.6Hz,ArCH_2), 3.38--3.47(m,4H,NCH_2), 4.10-4.24(m,3H,OCH_2-CHOH)), 6.89-6.93(d,2H,J=8.6Hz,ArH adjacent to O), 7.19-7.26(m,5H,ArH), 7.88-7.93 (d,2H,J=8.5Hz,ArH adjacent to carbonyl gr.)

MS(m/z) : 357($(M+1)^+$,35%)

Example 9: ***N -[2-hydroxy-3-(4-propionylphenoxy) propyl]-N'-2- phenethyl-urea (3g)***

To a stirred soln of 3-amino-(4-propionylphenoxy) propan–2-ol (0.223g, 1mmol.)in CH_3CN (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes .Mixture was stirred at 26°C for 15 hrs. till all the amine was consumed. Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield 79%. m p 94-95^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 1.17-1.24- (t,3H,J=7.3 Hz ,CH_3), 2.78-2.85(t,2H,J=6.8Hz,ArCH_2), 2.89-3.00(q,2H,J=7.3 Hz, $COCH_2$), 3.43-3.58(m,4H,NC H_2)), 3.96-4.05(m,3H,OCH_2-CHOH)), 6.89-6.94 (d,2H,J=8.8Hz,ArH adjacent to O), 7.15-7.77(m,5H, ArH), 7.91-7.95 (d,2H,J=8.8Hz,Ar H adjacent to cabonyl gr)

MS(m/z) : 371($(M+1)^+$,48%).

Example10: N-[3-(4-acetamidophenoxy)-2-hydroxy propyl]-N'-2- phenethyl-urea (3h.)

To a stirred soln of 1-(4-acetamidophenoxy)-3-amino propan-2-ol (0.224g, 1mmol.)in CH_3CN (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes .Mixture was stirred at 25°C for 11 hrs. till all the amine was consumed. Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield 64%. m p 150-151^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.11- (s,3H,$COCH_3$)2.75-2.82(t,2H,J=6.8Hz,$ArC\underline{H}_2$),3.28-3.51(m,4H,NCH_2), 3.87-4.01(m,3H,$OC\underline{H}_2$-C<u>H</u>-OH), 6.81-6.85(d,2H,J=8.8Hz,Ar H adjacent to O), 7.18-7.28(m,5H, ArH), 7.40-7.45 (d,2H,J=8.9Hz,Ar H adjacent to NH gr)

MS(m/z): 372 ($(M+1)^+$,70%).

<u>Example11</u>: N-[2-hydroxy-3-(2-methoxyphenoxy) propyl]-N'-2 phenethyl-urea(3i.)

To a stirred solution of 3-amino-1-(2-methoxyphenoxy) propan-2-ol (0.197g, 1mmol.)in CH_3CN (4mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 26°C for 12 hrs.till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$:MeOH (98:2)as the eluant, yield 38%, m.p. 80°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.75-2.82(t,2H,J=6.8Hz,$ArCH_2$)3.33-3.57(m,4H,NC H_2)), 3.79(s,3H,OCH_3), 3.96-4.04(m,3H,$OC\underline{H}_2$-C<u>H</u>OH)), 6.90-6.97(m,4H,ArH having OMe gr) 7.16-7.36(m,5H, ArH),)

MS(m/z) : 345($(M+1)^+$,100%).

<u>Example12</u>: N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-urea (3j):-

To a stirred soln of 3-amino-1-(4-methoxyphenoxy) propan-2-ol (0.197g, 1mmol.)in CH_3CN (4mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15 minutes .Mixture was stirred at 27°C for 8 hrs. till all the amine was consumed. Stirring discontinued, solid separated was filtered off and washed with hexane (10mL), dried. Yield-49%. m. p. 90°C.,

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.77-2.84 (t,2H,J=6.7Hz,$ArCH_2$), 3.42-3.48 (m,4H,NCH_2), 3.76 (s,3H,OCH_3), 3.87-3.90 (d,2H,J=6.46Hz,OCH_2), 4.00-4.02(m,1H,OHC<u>H</u>),6.82(s,4H,ArH contaning OMe gr),7.15-7.35(m,5H,ArH)

MS(m/z) : 345($(M+1)^+$,100%).

<u>Example13:</u> N-[3-(4-cyanophenoxy)-2-hydroxy propyl]-N'-2- phenethyl-urea.(3k):-

To a stirred solution of 3-amino-1-(4-cyanophenoxy) propan-2-ol (0.192g, 1mmol.) in 1,2-dichloroethane (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 26°C for 10 hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$:MeOH (98:2)as the eluant, yield 34%, m.p. 80°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.78-2.85(t,2H,J=6.7Hz,ArC<u>H</u>$_2$),3.28-3.55(m,4H,NCH_2), 3.95-4.10(m,3H,OC<u>H</u>$_2$-C<u>H</u>-OH),6.92-6.99 (d,2H,J=8.8Hz, ArH adjacent to O), 7.16-7.36(m,5H, ArH), 7.55-7.60 (d,2H,J=8.8Hz,Ar H adjacent to C≡N gr)

MS(m/z): 340($(M+1)^+$,93%).

<u>Example14</u>: ***N -[2-hydroxy-3-(2-methylphenoxy) propyl]-N'-2- phenethyl-urea (3l):-***

To a stirred solution of 3-amino-1-(2-methylphenoxy) propan-2-ol. (0.181g.,1mmol.) in CH_3CN (5mL) was added phenylethylisocyanate (0.221g., 1.5mmol.) slowly within 15min.. Mixture was stirred at 27°C for 13 hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$ as the eluant, yield - 37% .

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.20(s,3H,CH_3),2.76-2.83(t,2H,J=6.8Hz,ArCH_2),3.34-3.57(m,4H,NCH_2), 3.91-4.08(m,3H,OC<u>H</u>$_2$-C<u>H</u>-OH),6.79-6.90 (m,2H,4&6ArH), 7.10-7.32(m,7H, ArH).

MS(m/z): 329($(M+1)^+$,90%).

<u>Example15</u>: N-[2-hydroxy-3-(3-methoxyphenoxy) propyl]-N'-2-phenethyl-urea (3m.):-

To a stirred solution of 3-amino-1-(3-methoxyphenoxy) propan-2-ol (0.197g, 1mmol.)in CH_3CN (5mL) was added phenylethylisocyanate (0.221g, 1.5mmol.) slowly within 15min.. Mixture was stirred at 28°C for 11 hrs. till all the amine was consumed. Stirring discontinued, solvent distilled off, residual oil was washed with hexane (10mL). The crude material thus obtained was purified by column chromatography using $CHCl_3$:MeOH (99:1) as the eluant, yield 86%, m.p. 83-84°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.77-2.84(t,2H,J=6.8Hz,ArC<u>H</u>$_2$)3.35-3.49(m,4H,NCH_2)), 3.77(s,3H,OCH_3), 3.89-3.97(m,3H,OC<u>H</u>$_2$-C<u>H</u>OH)), 6.46-6.54(m,3H,ArH ortho to O) 7.13-7.30(m,6H, ArH),)

MS(m/z): 345($(M+1)^+$,100%).

<u>Example16</u>: N-[2-hydroxy-3-(4-trifluoromethylphenoxy)propyl)-N'-2-phenethyl-thiourea (3n)

To a stirred solution of 3-amino-1-(4-trifluoromethylphenoxy) propan-2-ol (0.235g, 1 mmol.)in CH_3CN (6mL) was added phenylethylisothiocyanate (0.163g, 1 mmol.) slowly within 15min.. Mixture was stirred at 25°C for 8 hrs. till all the amine was consumed Stirring discontinued, solid separated was filtered off and crystallized and recrystallised with dichloromethane and hexane, Yield 64 %., m p = 127°C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.89-2.95(t,2H,J=6.82Hz,ArC<u>H</u>$_2$), 3.69-3.8(m,4H,NCH_2) 3.95-4.02(m,2H,OC<u>H</u>$_2$), 4.2(m,1H, C<u>H</u>OH),6.93-6.97(d,2H,J=8.7Hz,ArH adjacent to O), 7.19-7.25(m,5H, ArH), 7.53-7.58 (d,2H,J=8.7Hz,ArH adjacent to CF_3)

MS(m/z): 399 ($(M+1)^+$,93%).

<u>Example 17:</u> ***N-[2-hydroxy-3-(4-propionylphenoxy) propyl]-N'-2- phenethyl-thiourea (3o)***

To a stirred solution of 3-amino-1-(4-propionylphenoxy) propan-2-ol (0.223g, 1 mmol) in CH_3CN (6mL) was added phenylethylisothiocyanate (0.163g, 1 mmol.) slowly within 15min.. Mixture was stirred at 26°C for 9 hrs. till all the amine was consumed. Stirring discontinued, solid separated was filtered off and crystallized and recrystallised with dichloromethane and hexane, Yield 64 %., m p = 125^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ1.17-1.24 (t,3H,J=7.2 Hz ,CH_3), 2.88-2.99(m,4H,$COCH_2$, ArC<u>H</u>$_2$), 3.63-3.79(m,4H,NCH_2)), 3.96-4.08(m,2H,OC<u>H</u>$_2$), 4.15-4.19(m,1H, C<u>H</u>OH), 6.88-6.93 (d,2H,J=8.8Hz,ArH adjacent to O), 7.19-7.33(m,5H, ArH), 7.90-7.95 (d,2H,J=8.8Hz,Ar H adjacent to cabonyl gr)

MS(m/z) : 387($(M+1)^+$,100%).

<u>Example 18:</u> N-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-N'-2-phenethyl-thiourea (3p)

To a stirred solution of 3-amino-1-(4-methoxyphenoxy) propan-2-ol (0.197g., 1 mmol.) in CH_3CN (5mL) was added phenylethylisothiocyanate (0.163g, 1 mmol.) slowly within 15min.. Mixture was stirred at 26°C for 9 hrs. till all the amine was consumed Stirring discontinued, solid separated was filtered off and crystallized and recrystallised with dichloromethane and hexane, Yield - 72 %, m p = 74-76^{0}C.

^{1}HNMR(200MHz,$CDCl_3$) : δ 2.87-2.94(m,2H, ArC<u>H</u>$_2$), 3.58-3.93(m,9H,NCH_2, OCH_3, OCH_2)),4.11 (m,1H, C<u>H</u>OH)), 6.81-6.82(s,4H,ArH containing OMe gr.), 7.22-7.26(m,5H, ArH),)

MS(m/z): 361($(M+1)^+$,100%).

Advantage

The pharmacological evaluation of the test compounds of general formula **3** was carried out by the following protocol.

The appetite suppressant activity of test compounds was tested on scheduled fed rat model of appetite. The study was conducted in adult male Sprague Dawley rats, weighing 175-200 g on arrival). The animals were housed in transparent cages of Bayer Makrolon type 3118 measuring 425 x 266 x 180 with floor area 800 cm^2. In each cage one rat was kept. A special fat rich diet (Diet # 12451, Research Diets, NJ, USA) was provided only for 3 h (11am - 2 pm) daily [no diet in rest of the period]. Water was provided for 24 h. Diet was

weighed prior to and after observation period by an electronic [Digital display] balance. Food intake was recorded by calculating the difference between prior and after weight of diet. Rats were weighed weekly after feeding. Rats were provided 16 g of diet daily and within 12-14 days animals achieved base line food intake (12-14 g) with gain in body weight (230 - 250 g) indicating adaptation to scheduled feeding. Only those rats that adapted to schedule feeding were used in the study. Rat showing significant less food intake and weight gain as compared to others was excluded from the study.

Thereafter, tests compounds dissolved in 10% DMSO aqueous solution and given in dose of 20 μmol / kg, by oral route. The test compounds were administered 30 min prior to food. Each test compounds were given in 5 rats. Diet and water was weighed at hourly interval in control and compound treated rats. During the period of feeding the gross behavior of rat was also observed.

The significance of difference between the food intake of treated and control groups was determined by unpaired Student's t test [Two tailed p value].

The compound **3a,** chemically, (N -[2-hydroxy-3-(4- trifluoromethylphenoxy) propyl]-N'-2-phenethyl-urea.,showed significant decrease of 41.42% in food intake as compared to food intake in the control group. The compound **3a** did not cause any significant change in water intake and gross behaviour. Moreover, the decrease showed by the compound **3a** was comparable with the decrease in food intake (38.57 %) caused by Sibutramine (20 μmol / kg, by oral route).

The compound **3j,** chemically, (N -[2-hydroxy-3-(4- methoxyphenoxy) propyl]-N'-2-phenethyl-urea.,showed significant decrease of 31.82% in food intake as compared to food intake in the control group. The compound **3j** did not cause any significant change in water intake and gross behaviour.

The compound **3n,** chemically, (N - [2-hydroxy-3-(4- trifluoromethylphenoxy) propyl]-N'-2-phenethyl-thiourea.,showed significant decrease of 28.4% in food intake as compared to food intake in the control group. The compound **3n** did not cause any significant change in water intake and gross behaviour.

The advantage of the present invention is that it provide a new class of compounds which are appetite suppressants and are simple than the existing standard drug sibutramine . The starting materials of the compounds of the present invention are cheap and are easily available .The process described here in simple economically feasible and ecofriendly .